



Docket No. 55591 RCE (71699)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Mail Stop Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**DECLARATION UNDER 37 CFR 1.131**

The undersigned declare as follows:

1. We are co-inventors of the above-identified patent application assigned to The Johns Hopkins University.
2. Prior to September 1998, we conceived of and then diligently reduced to practice the methods of introducing into endothelial cells of an autologous vein grafts from a mammal an effective amount of at least one nucleic acid encoding thrombomodulin (TM), NF- $\kappa$ B inhibitor, or a functional fragment of TM; provided that when the agent is thrombomodulin, the nucleic acid further encodes the NF- $\kappa$ B inhibitor, wherein the introducing is performed ex vivo or by direct injection into the graft, and transplanting the vein graft into the mammal as disclosed and claimed in the above-identified patent application.
3. We diligently worked to reduce the methods to practice until the filing of the provisional application on May 22, 2000.
5. Attached as Exhibit 1, Figures 1 – 20, are true and accurate copies of laboratory notebook records with dates deleted. The notebook records demonstrate the conception, reduction to practice and diligence from conception to the filing of the application. The exhibits show that the constructs for the expression were received prior to September 1998 representing proof of the conception of the methods of using thrombomodulin to prevent early vein graft thrombosis as described in paragraph 2 above (Figure 1).

6. Figure 2 shows successful adenovirus-mediated gene transfer of and expression of B-galactosidase marker genes in rabbit vein grafts. Figure 3 demonstrates that we were also transducing rabbit vein graft with the adenovirus vector expressing human TM (AdTMh5; Figure 3). Figure 4 demonstrates that we were able to quantify native TM expression in vein grafts by harvesting rabbit vein grafts at various time points. Figure 5 is a page from Dr. Antony Kim's notebook demonstrating TM expression over time (TMTC series of rabbits) outlining a visual scoring system devised to quantify native TM expression in rabbit vein grafts.

7. Figure 6, a page from Dr. Rade's notebook, depicts the continued generation of rabbits for TM quantification (C6W) and the transduction of rabbit vein grafts with control adenovirus (Adl312). Figure 7, a page from Dr. Kim's notebook, details a digital scoring system for TM expression in vein grafts. Figure 8, a log from Dr. Rade's notebook demonstrates transduction of a series of rabbit vein grafts with a different control adenovirus (AdRNull-1). Figures 9 and 10, from Dr. Kim's notebook, document TM expression in rabbit vein grafts using the digital imaging system.

8. Figure 11, a page from Dr. Rade's notebook, shows a series of rabbit vein grafts transduced with AdTMh5. Figures 12-14, from Dr. Kim's notebook, document the measurement of protein C activation and human TM protein expression in rabbit vein grafts transduced with either the AdTMH5 or control adenoviral vectors. Figure 15, a page from Dr. Richard Sohn's notebook, demonstrates the construction of an adenoviral vector expressing I $\kappa$ B, a potent NF- $\kappa$ B inhibitor. Figures 16, a page from Dr. Richard Sohn's notebook, shows the measurement of NF- $\kappa$ B activation in rabbit vein grafts.

9. Figure 17 documents the ability of the I $\kappa$ B adenovirus in preventing TM down-regulation in response to inflammatory cytokines. Figure 18, a page from Dr. Rade's notebook, details the group of rabbit vein grafts that were transduced with the I $\kappa$ B adenovirus. Figure 20 is

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U.S.S.N. 09/863,803  
Page 3

a figure resulting from data demonstrating that over-expression of I $\kappa$ B can reduce neointimal formation in rabbit vein grafts. Figure 21, a page from Dr. Sohn's notebook, shows that over-expression of I $\kappa$ B also effectively inhibits NF- $\kappa$ B activation in rabbit vein grafts.

10. We hereby further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both (18 U.S.C. 1001), and that such willful false statements may jeopardize the validity of the above-identified application or any patent issued thereon.

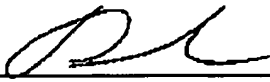
Date: 10/30/06

  
Jeffrey J. Rade

Date: \_\_\_\_\_

\_\_\_\_\_  
Antony Kim

Date: 10/30/06

  
Richard Sohn

Rade et al.  
U.S.S.N. 09/863,803  
Page 3

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Date: \_\_\_\_\_

\_\_\_\_\_  
Jeffrey J. Rade

Date: 2 Nov 2008

  
\_\_\_\_\_  
Antony Kim

Date: \_\_\_\_\_

\_\_\_\_\_  
Richard Sohn

Project No. 2Book No. 1TITLE Cloning of human Thrombomodulin into Adloxom Page No. 1Purpose: To make recombinant Adenovirus c human Thrombomodulin1. Obtained plasmid clone of human Tm from ATCC (ATCC#61348) FATCC 61348, 61349 - plasmid clone of human thrombomodulin <http://www.atcc.org/cgi-bin/SFgate?lang=828%20%2fpub%2fexfiles%2fMB-CLONE.TXT>Your query was:  
thrombomodulinConf. # SO44066\$105 + \$17.75 shipping**ATCC 61348, 61349 - plasmid clone of human thrombomodulin**

ATCC 61348, 61349 - plasmid clone of human thrombomodulin THBD

NAME: puc19TM15 (GDB:168893) (lambda HTm15)

DATABASE ACCESSION: DNA Seq. Acc. M16552

VECTOR: plasmid vector: pUC19

ORGANISM: THBD: Homo sapiens (human)

TISSUE: umbilical vein endothelial cells

GENE NAME: In insert THBD: thrombomodulin (GDB:119613)

CHROMOSOME: THBD 20 p11.2

DNA: THBD cDNA

CONSTRUCTION: Insert lengths (kb): THBD 3.70

Excise by: EcoRI or Sall

6.40

Sequence Position: DNA Seq. Acc.: M16552

MARKERS: ampr

DEPOSITORS: J. E. Sadler

REFERENCES: Biochemistry 26: 4350-4357, 1987

J. Biol. Chem. 264: 20705-20713, 1989 (CIT:381458)

Genomics 5: 649-650, 1989 (CIT:13744)

DESCRIPTION: Restriction digests of the clone give the following sizes

(kb): EcoRI- 3.7, 2.7; SacI- 6.5; Aval- 3.4, 2.0, 0.2; XbaI- 5.9,

0.54, 0.2, 0.1 (ATCC staff)

There is 64% homology between this probe and bovine thrombomodulin. A

single band of 3.7 kb is detected in human placenta and endothelial

cell poly(A)+ RNA. The insert includes 146 nt of 5'-noncoding

sequence, an open reading frame of 1725 nt and 1779 nt of 3'-noncoding

sequence including 40 nt of poly(A) tail. The insert contains the

following sites separated by (bp) (approx): EcoRI- 270- SmaI- 160-

PstI- 240- PstI- 210- PstI- 100- PstI- 530- KpnI- 310- PstI- 1080-

HindIII- 110- BamHI- 205- PstI- 475- EcoRI. (Biochemistry 26:

4350-4357, 1987)

GROWTH CONDITIONS: Medium 1227 37C

SHIPPED: 61348: freeze-dried Escherichia coli SURE

61349: dried purified DNA (200 ng)

PRICE CODE: 61348 D -- TIGR/ATCC SPECIAL COLLECTION OF HUMAN cDNA

CLONES

61349 D -- TIGR/ATCC SPECIAL COLLECTION OF HUMAN cDNA CLONES

To Page No. 1

Read &amp; Understood by me.

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Date

Recorded by



Figure 2

54

Project No. \_\_\_\_\_

Book No. \_\_\_\_\_

TITLE TX OF KASAT VIA GRAFT

From Page No. ①

PURPOSE: STAIN VIA GRAFT SCUMPS TO REGAL, FROST  
2% FARMING / 02% GUTTAUSUS, OR  
LONGITUDINAL PHOTOGRAPH & DIGITAL CAMERA

① BGAV-1

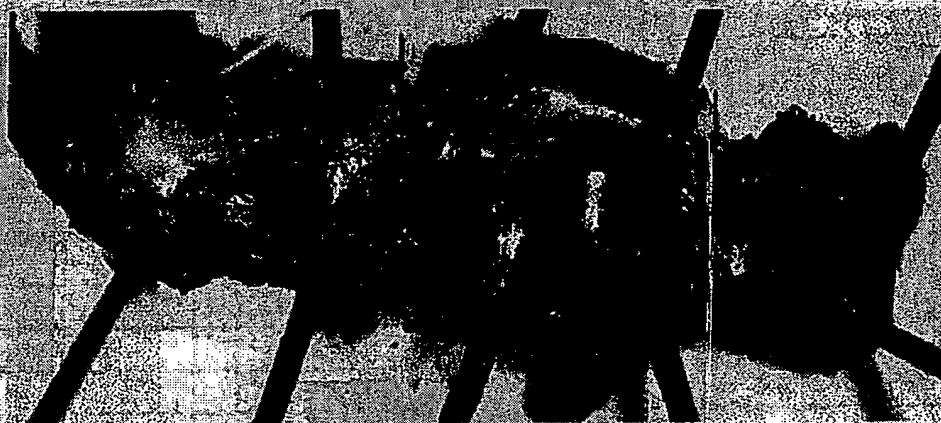
UNRAID

→ HARVEST

TX 200uQ m-199 + Ad CHIAZ (50uQ)

3000° PFU

→ 4x10<sup>9</sup> PFU (2x10<sup>10</sup> PFU/uQ)



BUT SURVEY - MOD CHANG

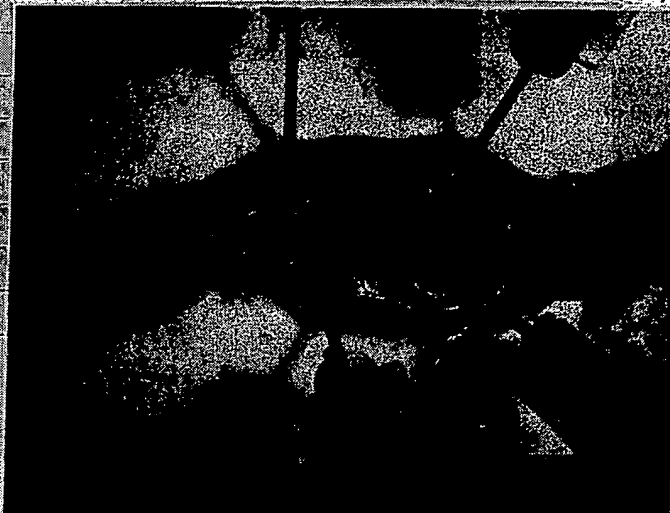
AMOUNT:

② BGAV-1

→

SAME UNRAID

UNRAID



10 Page no

Witnessed & Understood by me:

*[Signature]*

Date:

Invented by:

Date:

Recorded by:

Figure 3

day  
sac

TM#1

17 Views in 1025

H12

18 Views at 11:35

Signal

Clamp on 11:43

7.5 x

Ad FHHS

Clamp off 12:38

P: Fine up until clamp off  
 Distal good - no flow or leak. Cus II's  
 good but thin. A hand at  
 Clamps II revealed huge vent in proximal  
 graft

P: No p  
 Good  
 Perfect  
 Segment  
 8 cm  
 Good

~~3/11/19~~ 3/11/19

Repaired ed to ed a some narrowing  
 but still patent!

Pla Se  
 She

On figure of 8/10 at distal end  
 also - no narrowing

Segment left @ distal horn.

?? ? will see

Pla Se

See: Rabbit healthy - left open!



# Figure 4

86

Project No. \_\_\_\_\_  
Book No. \_\_\_\_\_ TITLE \_\_\_\_\_

From Page No. 22

GRAPHS CUT TO APR

SPECIMEN

SURV  
DATE

HARVEST  
DATE

DAYS

DOSS

AV

TWTC-1

5

0

25

TWTC-2

5

0

25

TWTC-3

5

0

25

TWTC-4

3

0

25

TWTC-5

3

0

25

TWTC-6

3

0

258

TWTC-7

1

0

208

TWTC-8

1

0

258

TWTC-9

1

0

258

TWTC-10

3

0

258

TWTC-11

3

0

258

=

TWTC-12A

10

0

Sum

TWTC-12B

10

0

Sum

TWTC-13

28cl

TWTC-14

TWTC-15

3

Sum

TWTC-16

3

Sum

=

TWTC-17

28cl

TWTC-18

14cl

0

Sum

TWTC-19

5cl

Sum

TWTC-20

1cl

Sum

TWTC-21

TWTC-22

AAUAC2-1

26cl

AAUAC2

AAUAC2-2

14cl

AAUAC2-3

7cl

TWTC-21

TWTC-22

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Date

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# Figure 5

TITLE

Robot Vein Graft Analysis (cont'd)

Project No. \_\_\_\_\_

Book No. \_\_\_\_\_

From Page No. \_\_\_\_\_

Grading System (cont'd)

## classification of thrombomodulin expression (intensity)

class

description

1+

trace, minimal

2+

patchy, scattered

3+

confluent, but not maximal intensity

4+

maximum intensity

CIRC.

day1

2

2

3

3

3

3

avg

2.666667

STD

0.57735

INTENS.

day1

2

2

2

2

02/03

2.5

avg

2.166667

STD

0.235702

Raw Data & Mean + S

(compiled E. Peter)

day3

2

2

2

2

avg

2

STD

0

day3

02/01

1.5

1

1

avg

1.25

STD

0.25

day28

4

4

3

3

3

3

3

3

3

3

3

3

avg

3.25

STD

0.381881

avg

STD

day5

3

3

2

2

02/03

2.5

avg

2.5

STD

0.408248

day5

2

2

2

2

2

2

avg

2

STD

0

control

4

4

4

4

4

4

4

4

4

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*[Signature]*

Date

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To Page

From Page No. 87

GNARIS SUT TO APB

SPURRING

SUNNY  
DATEWINDY  
DATE

285 C-32, LT-13  
 286 C-33, LT-14  
 287 C-34, LT-15

Adcon-1 2858

Adcon-2 2859

Adcon-3 2860

Adcon-4 2861

Adcon-5 2862

Adcon-6 - not sent

Adcon-7 2863

TmTC-22 2864

TmTC-24 2865

TmTC-21 3062

TmTC-23 3061

Fence Hand chains

Adcon-8 3205

Adcon-9 3206

TmTC-25 3207

C6W-2 3208

C6W-3 3209

C6W-5 3210

C6W-8 3211

C6W-10 3212

SUT TO APB

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To Page No. 92

Digital Imaging of Thrombomodulin in RVG's

Protocol: Hypothesis #1: TM protein expression decreases <sup>in RVG</sup> ~~when~~ <sup>when grafted into</sup> over time ~~when exposed to~~ arterial circulation;

Reason:

Hypothesis #2: TM protein reduction shifts the Thromboregulatory balance of normal vasculature to cause a more favorable Thrombotic state.

Reason:

Hypothesis #3: The prothrombotic state left by the reduction of TM is a factor in VG failure

Reason:

Adobe ① shoot images via DMC

② adjust brightness in order to control for all vessels

③ Mask the vessel ~ from endothelium

Sigma Scan ④ measurement setting - # of pixels (area) calibration 333 to

⑤ measure # of pixels on vessel endothelium (choose range for signal intensity threshold)

⑥ measure circumference of endothelium

Quattro ⑦ Record values including #pixels, circumference, + P/C





TM & F8-VWF

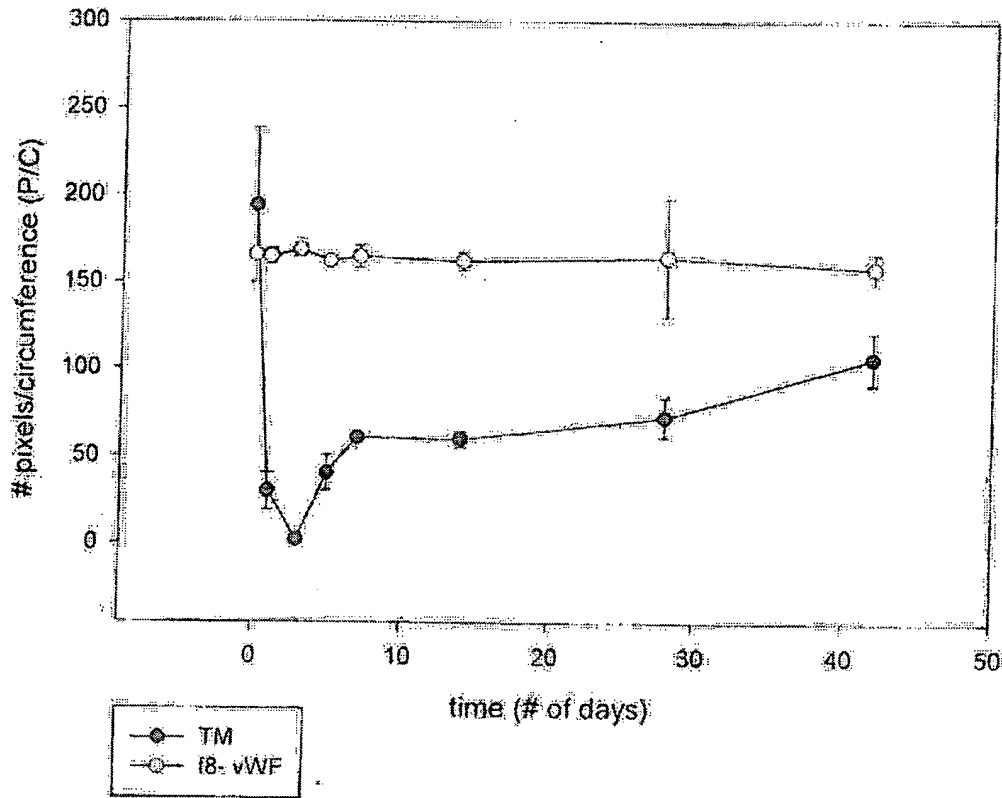
Project No. \_\_\_\_\_

Book No. \_\_\_\_\_

Figure 9

Page No. \_\_\_\_\_

# RVG Analysis



To Page No. \_\_\_\_\_

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Project No. \_\_\_\_\_

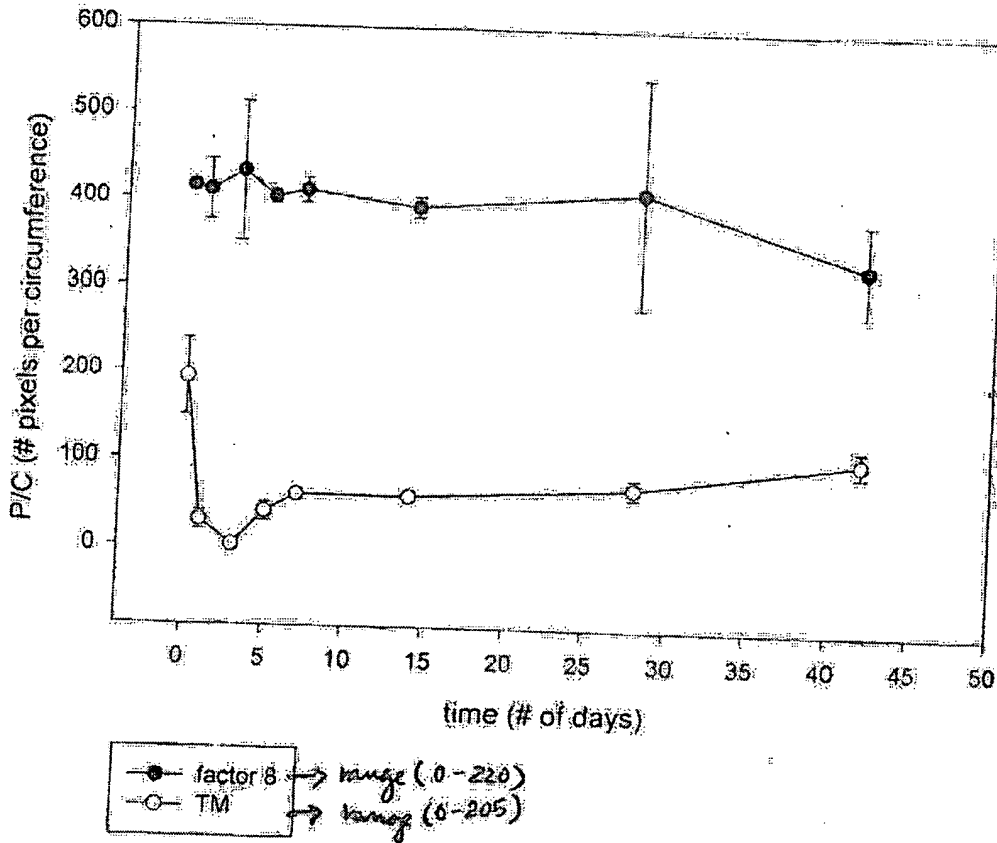
Book No. \_\_\_\_\_

Figure 10

Page No. \_\_\_\_\_

TM &amp; Factor 8 stains

TM and F8



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To Page No. \_\_\_\_\_

Figure 11

100

Project No. \_\_\_\_\_

Book No. \_\_\_\_\_

TITLE GRAFTS - SUT TO APID

From Page No. \_\_\_\_\_

=  
 Refusion Fixus 10% Form → 70% OTOH Site monophony  
 4017 Ad Tm HS #3  
 4018 Ad Tm HS #4  
 4019 Ad Tm HS #5  
 4020 Ad Tm HS #6  
 4021 Ad Tm HS #8  
 Ad Tm HS 3.75 x 10<sup>10</sup> p.p.h.

SUT

=  
 Refusion Fixus 10% Form → 70% OTOH Site monophony  
 4232 Ad Tm HS #12  
 4233 Ad Tm HS #15  
 4234 Ad Tm HS #16  
 Ad Tm HS 3.75 x 10<sup>10</sup> p.p.h.

HAND CHANGES TO APID

=  
 4508 C-89  
 4509 C-90  
 4510 Ad con -33  
 4511 Ad con -36  
 Ad Tm HS 3.75 x 10<sup>10</sup> p.p.h.  
 Refusion Fixus 10% Form → 70% OTOH Site monophony  
 SUT

=  
 4470 Ad Tm HS #14  
 4471 Ad con #21  
 4472 C-77  
 4473 C-81  
 Ad Tm HS 3.75 x 10<sup>10</sup> p.p.h.  
 Ad Tm HS 1  
 -  
 -  
 -

Refusion Fixus 10% Form → 70% OTOH Site monophony  
 SUT

=  
 4577 Ad con 35  
 4578 Ad con 42  
 4579 C-91  
 4580 C-92  
 4581 C-93  
 Ad Tm HS 3.75 x 10<sup>10</sup> p.p.h.  
 Ad Tm HS 1  
 -  
 -  
 -

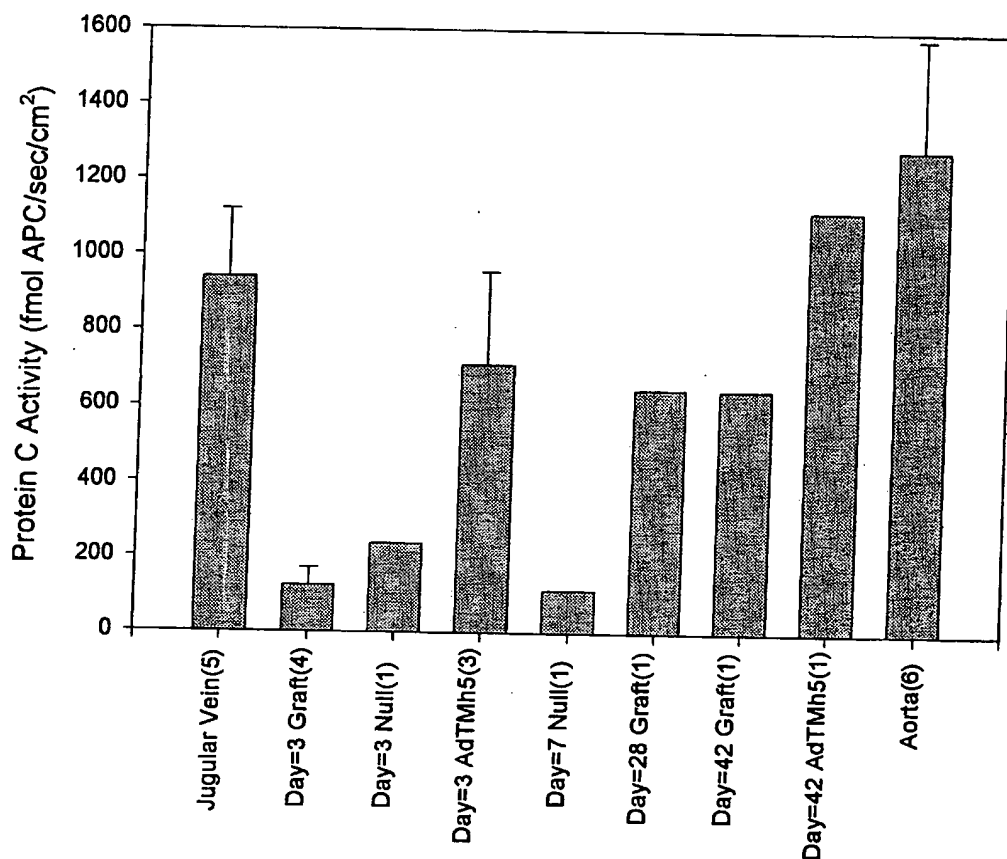
10% Form Fixus  
 Witnessed & Understood by me, \_\_\_\_\_ Date \_\_\_\_\_  
 SUT

To Page No. \_\_\_\_\_

From Page No. \_\_\_\_\_

Thurs.

Protein C Assay (Graph)



To Page No. \_\_\_\_\_

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Date

Recorded by



Fri

# Figure 13

① PC Activation Assay :

## PC Activation Assay AdTMh5 #25 (day 7)

[thrombin] nM	10	
[PC] uM	1	
	<u>RVG (7 day)</u>	<u>blank</u>
AdTMh5#25	522	16.29
AdTMh5#25 - blank	505.71	
avg.	505.71	16.29
aPC	0.468275065	
aPC(fmoles/min/cm2)	2498.2474717	

②

## aPC Standard Curve

<u>uM aPC</u>	<u>mOD/min</u>	<u>Regression Output:</u>	
0	0.857	Constant	0.001813143
0.05	55.4	Std Err of Y Est	0.006520627
0.1	107.4	R Squared	0.998984198
0.2	213.8	No. of Observations	7
0.3	311.6	Degrees of Freedom	5
0.4	428.4		
0.5	549.2	X Coefficient(s)	0.00092239
		Std Err of Coef.	1.31539E-05

To Page No. ....

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non TM ELISA for AdTMh5 + AdNull (American Diagnostica inc kit #831)

Figure 14

# THROMBOMODULIN ELISA

	<u>sample</u>	<u>OD (A450)</u>	<u>Dilution factor</u>	<u>TM</u>	<u>corrected TM</u>	<u>TM/BSA</u>
<u>AdTMh5</u>	<u>day 3</u>					
	TM9	1.21	20	3.20804	24.20000	39.18483
	TM11	1.23	50	3.27142	163.57088	185.85785
	TM23	1.359	50	3.68020	184.00989	108.11640
	<u>day 7</u>					
	TM25	3.166	50	9.40629	470.31439	354.42972
	TM27	2.466	50	7.18810	359.40506	149.04811
	<u>day 14</u>					
	TM19	0.681	10	1.53173	15.31726	9.36070
	TM20	0.781	10	1.84861	18.48609	7.40715
	TM21	0.791	10	1.88030	18.80298	9.96799
	<u>day 28</u>					
	TM22	2.187	50	6.30400	315.19977	231.53710
	TM29	1.162	50	3.05594	152.79683	66.64825
	TM30	1.148	50	3.01157	150.57865	65.59129
	<u>day 42</u>					
	TM18	0.437	10	0.75853	7.58529	11.80432
<u>AdNull</u>	<u>day 3</u>					
	NULL23	0.187	2	0	0	0
	NULL28	0.16	2	0	0	0
	NULL43	0.204	2	0	0	0
	<u>day 7</u>					
	NULL25	0.195	2	0	0	0
	NULL27	0.206	2	0	0	0
	NULL31	0.201	2	0	0	0
	<u>day 14</u>					
	NULL34	0.258	2	0	0	0
	NULL37	0.193	2	0	0	0
	NULL40	0.149	2	0	0	0
	<u>day 28</u>					
	NULL29	0.172	2	0	0	0
	NULL36	0.194	2	0	0	0
	NULL39	0.165	2	0	0	0
	<u>day 42</u>					
	NULL19	0.181	2	0	0	0
	NULL22	0.197	2	0	0	0
	NULL24	0.188	2	0	0	0

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From Page No. \_\_\_\_\_

Primer "RSV1": AGCACC GTG CAT G CC GATT CGT TGA

To insert present, then fragments → ~ 1300 - 1400 bp.

PCR: ① RSV WT ② RSV ΔS ③ pAdlox R, 1KB WT

Viral plating: overlaid  
2nd layer MEM/agarose.



No insert in viruses  
① Ctrl (shuttle plasmid)  
verify PCR works

→ tested out plating for CMV, ΔS 1KB

- ① Plaque 6 plaques are inoculated 6 well-plate & 293 cells.
- ② Thawed CPE 8 cells
- ③ Digested [pAdlox R 1KB WT / pAdlox R 1KB ΔS] on hopes that recombination is 45% would be more efficient.



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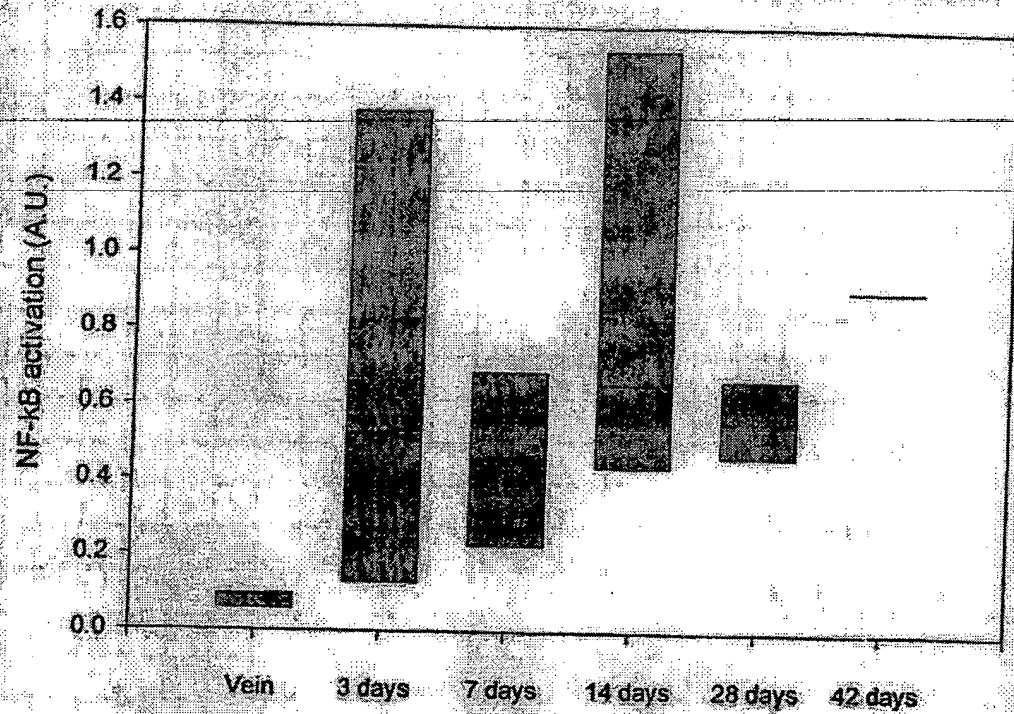
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Invented by \_\_\_\_\_

Date \_\_\_\_\_

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# Vein Grafting and NF-kB Activation: Adenoviral Expression of Thrombomodulin



Thawed 293 cells

↓  
in medium

500 HUVEC : 50 plates 60mm  
T plate 150mm

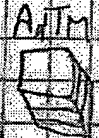
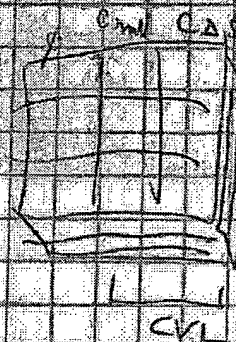
↓  
nearly confluent → infecting + virus

\* 90 min

↓  
Cover =

Additional 2.5 ml

ph



100 Mo  
(5ml  
in 60ml)

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Date

Invented by

Date

Recorded by



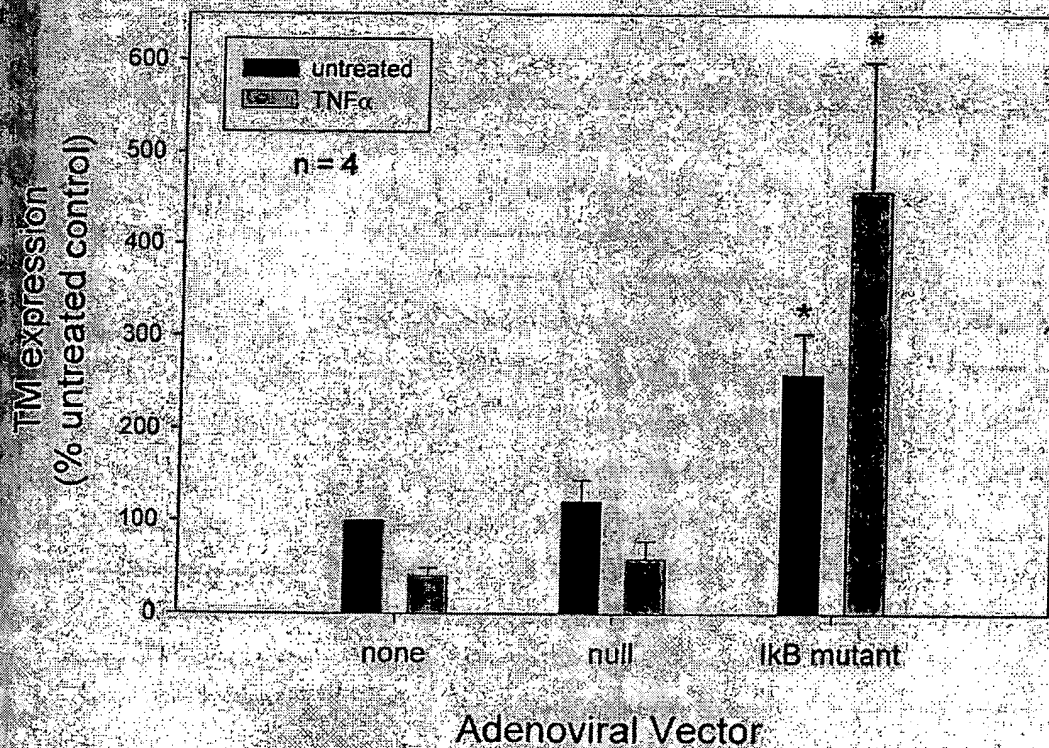
Project No..

Book No..

Figure 17

	ctrl	TNF	null	null + TNF	IkBm	IkB + TNF
gel 1	598	274	519	148	1262	1290
gel 2	249	63	430	228	831	1826
gel 3	286	84	423	265	950	1918
gel 4	1088	668	841	288	1754	2330
as % ctrl	100	46.8194	86.7893	24.74916	211.0368	215.7191
	100	25.3012	172.6908	91.56627	333.7349	733.3333
	100	29.37063	147.9021	92.65734	332.1678	670.6294
	100	61.39706	77.29779	26.47059	161.2132	214.1544
mean	100	40.47207	121.17	58.86084	259.5382	458.459
S.D.	0	16.53125	46.46073	38.40392	87.17875	282.3589
S.E.M.	0	8.265623	23.23036	19.20196	43.58938	141.1794
t-test						
vs. control			0.397268		0.010579	
vs. null					0.031108	
vs. null-TNF						0.030975

### Inhibiting NF-kB Activation In HUVEC Upregulates TM and Prevents TM Downregulation By TNF $\alpha$



Recorded by

Figure 18

108

Project No. \_\_\_\_\_

Book No. \_\_\_\_\_

TITLE GNAPS SUT TO APID

From Page No. 103

10% Form Fixer → 30% Wash

<u>RA/RTT</u>	<u>SUNNY</u>	<u>H.A. VLP</u>	<u>V/LVLS</u>	<u>DOSE</u>	<u>Time</u>
1KB-2 6274					
1KB-3 6275					
1KB-9 6276					
1KB-10 6277					
1KB-11 6278					
1KB-12 6279					
1KB-13 6280					

Fixation

6470 1KB 14  
6471 1KB 16  
6472 1KB 17  
6473 1KB 18

SUNNY

H.A.

6700 1KB 14  
6471 1KB 16  
6472 1KB 17  
6473 1KB 18

SUNNY

GNAPS

Ag/RTT  
3.75 Yrs

Time  
(blue)

SUT APID

To Page No. \_\_\_\_\_

Witnessed & Understood by me, \_\_\_\_\_

Date \_\_\_\_\_

Invented by \_\_\_\_\_

Date \_\_\_\_\_

Recorded by \_\_\_\_\_

Figure 19

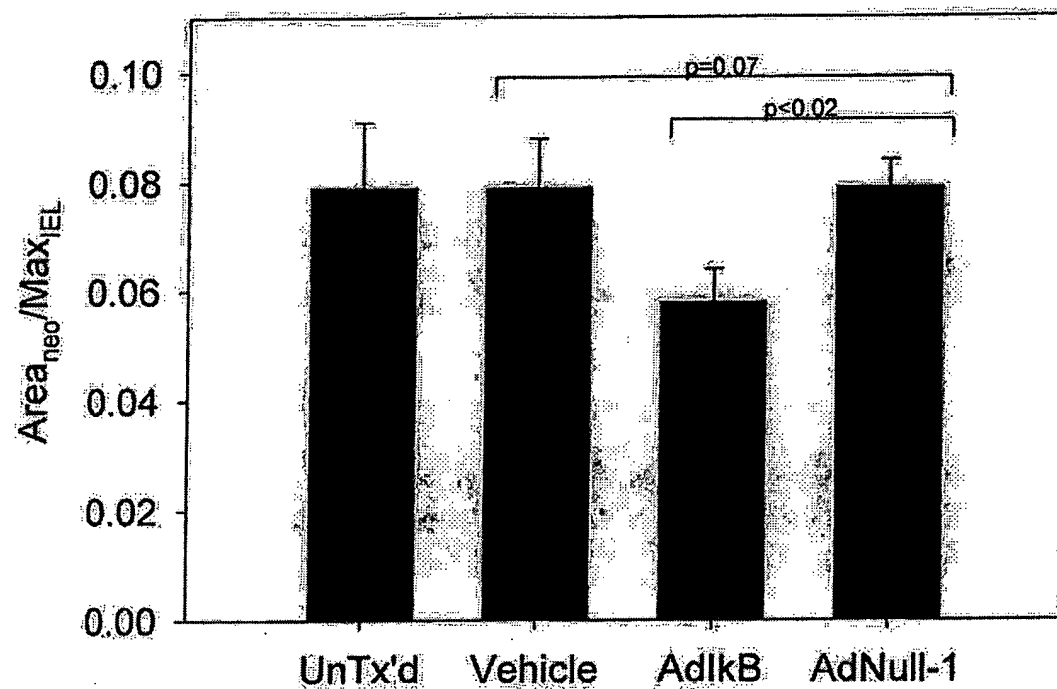
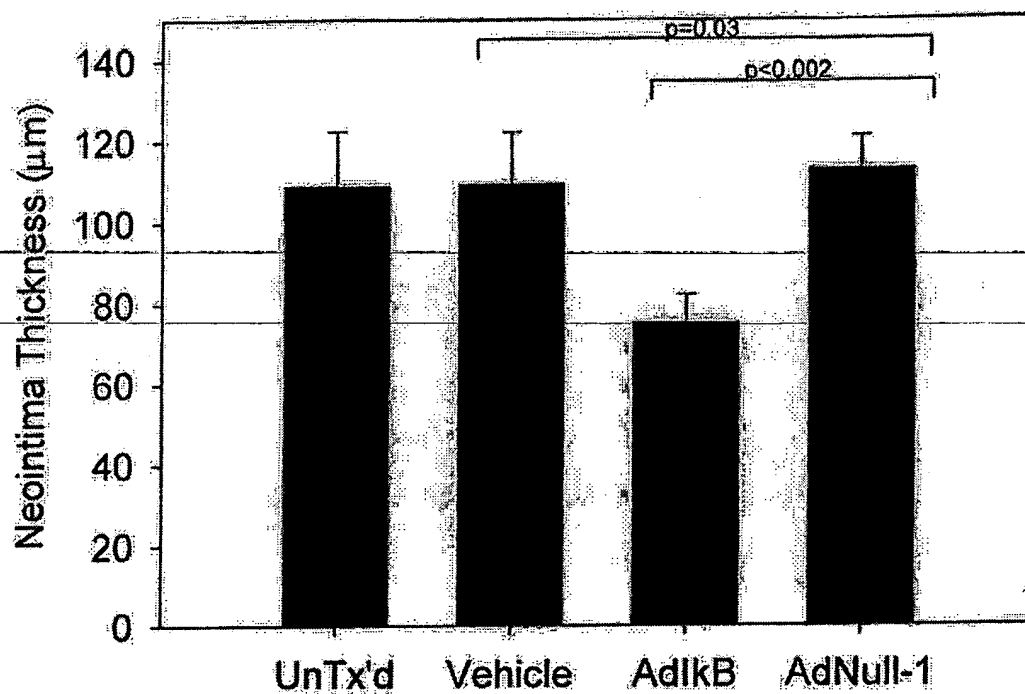
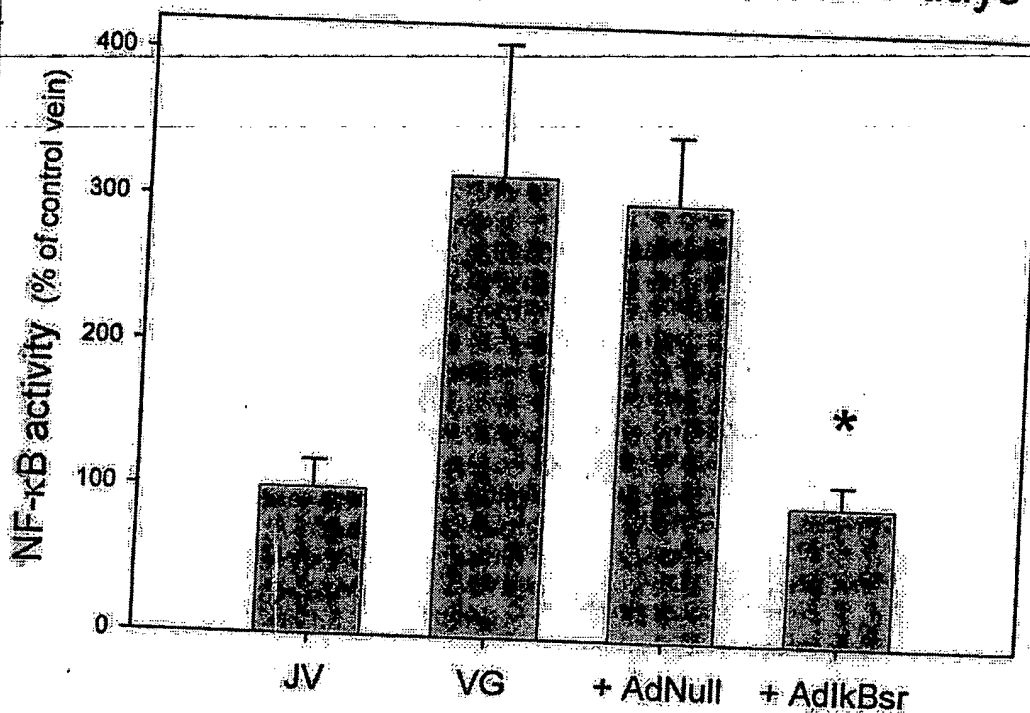


Figure 20

NF- $\kappa$ B Activity in Vein Grafts at 7 days

\*  $P=0.014$ , as compared to AdNull-transduced vein graft

Restatement of Transducing Nucleic Acid is as follows: *[Signature]*

① Jet PEI - RGD (Qbiogene Molecular Biology)

② Tfx - 50 (Promega)

Witnessed &amp; Understood by me, \_\_\_\_\_

Date \_\_\_\_\_

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